Regenerative Therapy 18 (2021) 88–96

Contents lists available at ScienceDirect

Regenerative Therapy

journal homepage: http://www.elsevier.com/locate/reth

Review

Research progress in decellularized extracellular matrix-derived hydrogels

Wenhui Zhang [a], Aoling Du [b], Shun Liu [a], Mingyue Lv [c], Shenghua Chen [a, *]

[a] Institute of Applied Anatomy and Reproductive Medicine, Hengyang Medical College, University of South China, Hengyang, Hunan 421001, China
[b] Medical College, Hubei University of Arts and Science, Xiangyang, Hubei 441053, China
[c] Anesthesia Class 1 of Chuanshan College, South China University, Hengyang, Hunan 421001, China

ARTICLE INFO

Article history:
Received 15 January 2021
Received in revised form
21 March 2021
Accepted 27 April 2021

Keywords:
Decellularization
Extracellular matrix
Hydrogel
Tissue engineering
Regenerative medicine

ABSTRACT

Decellularized extracellular matrix (dECM) is widely used in regenerative medicine as a scaffold material due to its unique biological activity and good biocompatibility. Hydrogel is a three-dimensional network structure polymer with high water content and high swelling that can simulate the water environment of human tissues, has good biocompatibility, and can exchange nutrients, oxygen, and waste with cells. At present, hydrogel is the ideal biological material for tissue engineering. In recent years, rapid development of the hydrogel theory and technology and progress in the use of dECM to form hydrogels have attracted considerable attention to dECM hydrogels as an innovative method for tissue engineering and regenerative medicine. This article introduces the classification of hydrogels, and focuses on the history and formation of dECM hydrogels, the source of dECM, the application of dECM hydrogels in tissue engineering and the commercial application of dECM materials.

Contents

* Corresponding author.
E-mail address: chenshenghuaa@163.com (S. Chen).
Peer review under responsibility of the Japanese Society for Regenerative Medicine.

https://doi.org/10.1016/j.reth.2021.04.002

1. Introduction

Extracellular matrix (ECM) is a complex network of macromolecular substances synthesized and secreted by various tissues and cells in the body, such as fibroblasts, mesenchymal cells, and epithelial cells, which are distributed and aggregated on the cell surface and intercellular substances. ECM forms the cell-based skeleton of tissues and organs and supports and connects the tissue structures, regulates the tissue development, and forms the microenvironment required for cell growth. ECM has a significant impact on cell behavior, including adhesion, differentiation, proliferation, migration, and functional expression [1]. ECM plays an important role in tissue development, homeostasis and disease [2].

In some diseases, the tissues or organs must be replaced due to severe damage [3]. However, insufficient donor sources and rejection after transplantation have restricted the application of this treatment [4]. Investigation of the composition and function of ECM in various tissues and imitation and construction of biological scaffolds with high biomimetic properties have become important areas in the field of tissue engineering [5]. Hydrogel can simulate the water environment of human tissues, has good biocompatibility, and can exchange nutrients, oxygen, and waste with the cells. Currently, hydrogel is an ideal biological material for tissue engineering [6]. Studies by Badylak et al. have shown that decellularized biological scaffolds have good conservation between the species and are well tolerated by heterogeneous hosts thus effectively reducing immune rejection and promoting structural remodeling [7]. The decellularized scaffolds of the natural tissues obtained by the decellularization methods, such as physical, chemical, and enzymatic methods [8–11], are freeze-dried, ground, and enzymatically digested to form a decellularized extracellular matrix (dECM) hydrogel that retains the structural characteristics and stimulatory properties of the hydrogel responsiveness while retaining the function of ECM. The progress in the development of the methods of hydrogel formation by ECM bio-scaffolds has expanded potential applications of the hydrogels in vitro, in vivo, and in clinical practice [12]. This article reviews the types of hydrogels, the history and formation of dECM hydrogels, the source of dECM, the applications of dECM hydrogels in tissue engineering, the commercial application of dECM materials, and future prospects in the field.

2. Hydrogels

Hydrogel is a polymer with three-dimensional network structure that has hydrophilic groups, can absorb a large amount of water or biological fluids, and swells in the presence of water but is insoluble in water. Hydrogels can maintain a unique three-dimensional network structure and polymer chain network. Hydrogels interact with water or biological fluids by capillary force, penetration force, and hydration force, and these forces can cancel each other [13]; and it affects the swelling of hydrogels driven by osmotic pressure and Gibbs–Donnan effect. Hydrogels can simulate the natural microenvironment of the cells. Therefore, hydrogels are one of the most common tissue engineering scaffolds [14]. The application of the hydrogels was started by Wichterle and Lim [15] who successfully prepared hydrogels by polymerizing 2-hydroxyethyl methacrylate in 1954, and made the first contact lens in history. Good uniformity and operability of the hydrogels enable expanded applications in various fields.

There are many types of hydrogels. Hydrogels can be divided into natural, synthetic, and hybrid hydrogels.

Natural hydrogels are mainly composed of collagen [16], gelatin [17], hyaluronic acid [18,19], fibrin [20], agarose, dextran, alginate [21], chitosan [22], and other natural polymers. The structure and composition of natural hydrogels are similar to those of the natural extracellular matrix and have good biocompatibility and biofunctionality [23]. However, natural hydrogels also have some shortcomings, such as batch differences in the structure and performance during preparation, potential immunogenicity, and relatively poor mechanical properties, which limit their applications [24–26].

Synthetic hydrogels are mainly composed of polyethylene oxide, polyethylene glycol (PEG) [27–29], polyvinyl alcohol [30], polyacrylamide, N-isopropylacrylamide (PNIPAM) [31,32],etc. The composition can be molecularly customized according to the type of hydrogel required for block structure, molecular weight, mechanical strength and biodegradability [33]. However, synthetic hydrogels are mainly crosslinked by free radical initiators and crosslinking agents. The use of free radical initiators and crosslinkers has many disadvantages, such as residual unreacted monomers, and residual crosslinkers or initiators, which can cause inflammation or cytotoxicity.

Composite hydrogels are prepared by combining the characteristics of synthetic and natural polymers and are known as hybrid hydrogels. Hybrid hydrogels can be prepared by covalent coupling of synthetic and natural polymers by chemical coupling or polymerization. Synthetic polymers provide adjustable physical properties, and natural polymers provide special biological functions [34]. This method is advantageous because it does not require complex bioconjugation during preparation of bioactive hydrogels unlike the methods used to prepare bioactive synthetic polymers. However, use of animal-derived natural polymers can cause immunogenic reactions and infections.

3. dECM hydrogels

Properties of an ideal bioactive hydrogel scaffold should be similar to the structure and biological properties of natural tissue ECM. Current bioactive polymer hydrogels are limited in simulation of various biological functions and mechanical properties of ECM. Acellular matrix is a natural scaffold prepared from the tissues or

organs by removal of cellular components and retains the three-dimensional structure of the tissues or organs and some natural fiber components, such as collagen fibers; the scaffold is biologically active, biocompatible, and nonimmunogenic. dECM hydrogel retains a number of cell growth factors, such as fibroblast growth factor, transforming growth factor, and hepatocyte growth factor, which can enhance the growth, migration, proliferation, differentiation, and angiogenesis of the seed cells. This "real-time interaction" with the seed cells can reshape the structure of the tissues and organs and is important for the regeneration and functional repair of the tissues and organs.

3.1. History of dECM hydrogel

In clinical and preclinical research, biological scaffolds composed of extracellular matrix (ECM) have been used to promote the repair and reconstruction of various tissues. The clinical use of such scaffolds may be limited by the geometric and mechanical properties of the tissue or organ from which the ECM is harvested. The injectable gel form of ECM can potentially conform to any three-dimensional shape, and it can be delivered to the site of interest through minimally invasive techniques [35]. Therefore, gradual advancement of the decellularization technology and improvement in the ability of decellularized extracellular matrix (dECM) to form hydrogels resulted in innovative applications of dECM hydrogels in tissue engineering and regenerative medicine [36]. After Badylak and coworkers reported the preparation of porcine bladder acellular matrix hydrogel in 2008, the heart [37–39], kidney [40,41], liver [42], pancreas [43], esophagus [44], submucosa of the small intestine (SIS) [45,46], meniscus [47,48], nerves [49–51], fat [52,53], and other tissues have been decellularized and gelled. Thus, dECM hydrogel has broad application prospects in clinical practice.

3.2. dECM hydrogel formations

Biological scaffolds derived from ECM are the natural components of the tissues that have been decellularized to retain the inherent structural and chemical integrity of the original tissues. The formation of extracellular matrix-derived hydrogels after decellularization is based on collagen self-assembly and is influenced by glycosaminoglycans, proteoglycans, and various proteins. Usually, a decellularized biological ECM scaffold is freeze-dried and ground into a powder, which is digested and dissolved in an acidic solution with an acid protease in a certain proportion to prepare a homogeneous solution. Then, the solution temperature, salt ion concentration, and pH are changed or a crosslinking agent is added to induce crosslinking to form a gel [35,54]. Freytes [35] et al. prepared the solution of porcine bladder dECM by freeze-drying, grinding, hydrochloric acid-pepsin digestion in solution, and magnetic stirring, and adjusted pH of the porcine bladder dECM solution to neutral (pH $\approx$ 7.4) with sodium hydroxide. The salt ion concentration in the solution was changed to form a pregel, and the hydrogel was formed by heating to 37 °C. Recently, Badylak and coworkers proposed a new method of preparation of ECM hydrogels using ultrasonic cavitation. Crushed ECM was used as the starting material; ECM was resuspended in a neutral buffered salt solution and dissolved by sonication at 20 kHz. The temperature of the ECM solution was reduced below 25 °C to induce rapid gelation [55]. Pregelation of the dECM solution is the key step in the formation of a dECM hydrogel. Clinicians can inject a dECM pregel into a surgical site. At human body temperature (37 °C), dECM pregel can quickly form a dECM hydrogel.

3.3. Source of dECM

3.3.1. Cell source

The cell-derived matrix (CDM) contains a complex and organized mixture of macromolecules that can mimic all aspects of the natural tissue microenvironment [56]. Both primary cells and cell lines have been used to produce CDM. Primary cells harvested directly from tissues without passage are generally considered to be ideal cell sources for tissue engineering and biomedical applications, because they are very similar to their natural in vivo phenotypes, and can be said to produce more similar to the natural microenvironment the capacity of the substrate [57]. Mesenchymal stem cells are easily obtained cells and are usually used to prepare cell-derived ECM because they have the ability to deposit ECM that simulates various tissues (such as bone, cartilage, fat) according to culture conditions, and their applications in tissue engineering The universal use [58]. One of the main disadvantages of cell-derived dECM is that CDM generally has poor mechanical properties [59].

3.3.2. Animal source

The sources of autologous and allogeneic tissues are extremely limited. Xenotransplantation is still a suitable solution to overcome the shortage of human tissues [60]. The acellular extracellular matrix of xenogenes has become a major theme of today's tissue repair technology research. Various tissues from different animals have been widely used to create dECM, such as the bladder and heart of pigs [61,62], tendons of cattle [63], lung and kidney of goat [64,65], and liver and lungs of rats [66,67]. A major source of heterogeneous DECM is pigs [68–70]. The use of pig tissues and organs is superior to other animal tissues and organs in many aspects. Organs from pigs are readily available and available in larger quantities than from other animals [60]. Due to its high reproductive capacity and large number of offspring, pigs have always been the number one choice when it comes to DECM that provides tissues and organs [71], but the risk of human infection with porcine endogenous retrovirus (PERV) is inevitable [72]. In addition, the difference in source tissues may affect the composition, degradation rate and mechanical properties of dECM [73].

3.3.3. Human source

In order to avoid the spread of disease from animals and the xenogeneic dECM obtained from animals may contain residual contamination and immunogenicity, human tissues will be the best choice for dECM for clinical applications [74,75]. Human-derived dECM can be obtained from cadavers, diseased or damaged tissues and organs of patients, and tissues donated from human tissue biobanks [75,76]. Various tissues and organs from the human body have been used to create dECM. For example, the entire heart [77,78], cartilage [79–81], ovarian tissue [82], adipose tissue [83,84], pancreas [85], kidney [86], liver [87], skin [88], teeth [89] and lungs [90] have been successfully decellularized.

4. Application of dECM hydrogels in tissue engineering

dECM hydrogels have the following advantages. (1) Injectability. Viscous fluid pregel can be injected with a catheter or a syringe and polymerized at physiological temperature to form a hydrogel conforming to the shape of a defect site. (2) dECM hydrogels have inherent biological activity of the natural matrix [91]. (3) dECM hydrogels do not contain immunogenic cellular material. (4) Adjustability of mechanical properties. Mechanical properties of dECM can be controlled by changing the concentration of a hydrogel or by crosslinking. (5) Gelled dECM has a three-dimensional structure suitable for cell growth [92]. (6) dECM hydrogels are modifiable and can support the cells, therapeutic

drugs, or other biologically active molecules. (7) Machinability of dECM hydrogels. 3D geometric shapes can be customized by 3D printing [49]. Therefore, dECM is widely used in in vitro and in vivo applications as shown in Fig. 1 below.

4.1. In vitro applications of dECM hydrogels

ECM hydrogels derived from decellularized tissues can be used for in vitro vascular network reconstruction [93] and as the substrates for in vitro cell culture systems [41], bioinks [14,94] and organoid derivatives [45] to provide guidance for the cells. The growth environment maintains and enhances the tissue-specific cell phenotypes, induces the chemotaxis of lineage-oriented progenitor cells, and regulates cell proliferation and differentiation [95–97].

4.1.1. Substrates for cell culture systems

The study of cell behavior has always been a challenge. When the cells are removed from the 3D environment of the tissue, they lose contact with the ECM and basement membrane and change their behavior. Therefore, close attention is paid to optimization of the 3D culture systems to simulate the processes that cells may undergo in the body. Some studies have used human glomerular endothelial cells (GEnCs) as a model cell type to investigate the interaction of the cells with kidney dECM hydrogel. The GEnC line is derived from endothelial cells isolated from the glomerulus. Unlike primary cells that are difficult to expand in the culture and lose important phenotypic characteristics over time, conditionally immortalized GEnCs are cultured at an appropriate temperature. Their expansion can be maintained; however, transfer to an inappropriate temperature stops the expansion and initiates gradual maturation. In vitro studies demonstrated that kidney dECM hydrogels can be used as biocompatible substrates to support the attachment, survival, and proliferation of human GEnCs. These hydrogels are formed under mild conditions and physiological temperature; hence, they can be used for cell encapsulation. Human GEnCs have high viability after encapsulation in a kidney dECM hydrogel (2.5 mg/mL) [41]. In Matrigel has been demonstrated to be the most effective culture substrate in terms of maintaining differentiated gene expression and function. Matrigel is a basement membrane matrix derived from EHS mouse sarcoma. An ECM gel form derived from pig liver supports human hepatocyte function at a level equivalent to that of Matrigel in vitro [98]. These studies indicate that dECM hydrogels can be used as an ideal 3D culture system to create an environment that can guide cell growth and regulate cell proliferation and differentiation.

4.1.2. In vitro reconstruction of the biliary tree

The bile duct tree is an important part of transplantable human liver tissue. Its finer branches are complex and have heterogeneous structure and function. They cannot be cultivated artificially and can only be regenerated by innate development. The extracellular matrix (ECM) of the developing liver plays an indispensable role in the formation and maturation of the bile duct tree. Primary bile duct cells have a certain degree of in vitro morphogenesis to generate cholangiocytes. The bile duct cells (SV40SM44) can be encapsulated in the liver dECM gel. The have high viability and are assembled into the complex branched duct-like structures on an unprecedented scale. Liver dECM hydrogel induces the formation of a complex bile duct network in vitro by immortalized mouse small bile duct epithelial cells (cholangiocytes) [93]. In Moreover, inherent biological activity of dECM hydrogels and 3D printing of sacrificial biological materials can be used to create a spatially defined 3D bile duct tree by changing the geometry (width and angle) of the dECM structure to guide the orientation of the bile duct tree [99]. These results demonstrate the effect of dECM hydrogel on the formation of bile duct network and suggest that dECM hydrogels can be used in the future for intrahepatic bile duct tissue engineering.

4.1.3. Organoid cultures

Organoids are three-dimensional multicellular constructs, which are a promising source of the cells for tissue repair and can be used for tissue regeneration and treatment in various disease models. Usually, organoids can be cultured in 3D hydrogel systems. Intestinal ECM gel can support the culture of intestinal organoids and cells from other endoderm-derived tissues (such as liver, stomach, and pancreas) [45]. Additionally, comparison of organoids without a hydrogel with organoids in dissolved LEM, 3D collagen gel organoids, and traditional 2D cultures indicated that self-contained 3D liver-derived dECM hydrogel LEM gel can organize human liver cancer (Huh7) cells, bone marrow MSCs, and umbilical vein endothelial cells (HUVEC) to create liver organoids. Epithelial phenotype of hepatocytes was characterized by higher cell viability, and the expression and function of hepatocyte-specific genes was significantly increased [42]. The Thus, dECM hydrogel can provide support for organoid cultures.

4.1.4. Decellularized ECM-derived bioinks

3D bioprinting is a powerful technique for engineering tissues used to study cell behavior and tissue properties in vitro [100–102]. One of the main prerequisites in 3D bioprinting is finding an appropriate bioink that provides a tissue-specific microenvironment supporting the cellular growth and maturation [103–106].

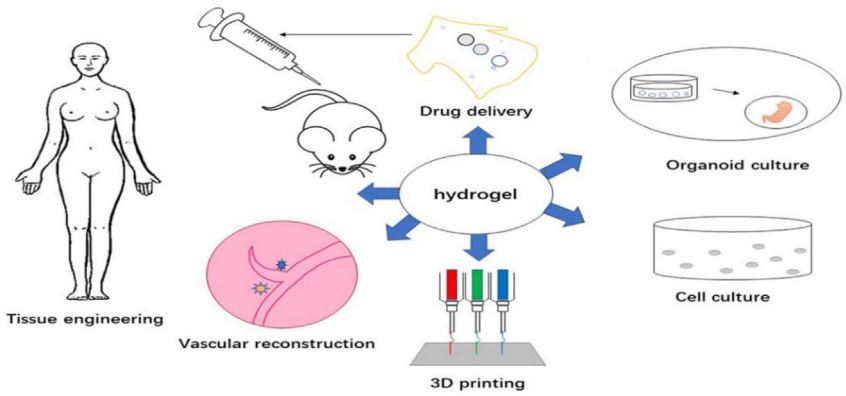

Fig. 1. Application of dECM hydrogels in tissue engineering.

Bio-based materials that support cellular adhesion, differentiation, and proliferation – including gelatin, hyaluronic acid, collagen and alginate have been successfully used as bioinks [107–109]. In particular, decellularized extracellular matrix (dECM) has become a promising material with the unique ability to maintain both biochemical and topographical micro-environments of native tissues [14,110–112]. Studies have shown that the photo-crosslinkable kidney ECM-derived bio-ink (KdECMMA) can provide a kidney-specific microenvironment for kidney tissue bioprinting. Porcine whole kidneys are decellularized through a perfusion method, dissolved in an acid solution, and chemically modified by methacrylation. A KdECMMA-based bioink is formulated and evaluated for rheological properties and printability for the printing process. The results show that the bioprinted human kidney cells in the KdECMMA bioink are highly viable and mature with time. Moreover, the bioprinted renal constructs exhibit the structural and functional characteristics of the native renal tissue. The potential of the tissue-specific ECM-derived bioink is demonstrated for cell-based bioprinting that could enhance the cellular maturation and eventually tissue formation [113]. The above research shows that the 3D bioprinting strategy using dECM hydrogel as bio-ink has great potential in bioengineering functional tissue constructs for future regenerative medicine applications.

The latest progress in the extraction and purification of decellularized extracellular matrix (dECM) from healthy or malignant tissues has opened up a new way for engineering physiology to simulate 3D in vitro tumor models. Research has shown that 3D bioprinted self-gelling mammary adipose tissue-derived dECM-based hydrogels from both rat and human sources enabled the generation of organotypic constructs conjugating distinct breast cancer cells, demonstrating the importance of using tissue specific ECM as a basis for TME-ECM cancer cell interaction analysis and the need for carefully establishing comparisons with observations derived from other non-tissue-specific ECM-derived biomaterials [114]. This is of great significance for understanding the role of ECM in controlling cell fate for developmental biology, tissue engineering and cancer treatment [115].

4.2. In vivo applications of dECM hydrogels

ECM hydrogels have been extensively used in many preclinical studies to promote tissue repair after an injury, including the heart, lung, brain, nerves, and colon.

4.2.1. Heart

Cardiovascular disease is a common serious threat to human health. More than half of patients who die of cardiovascular disease have myocardial infarction. The pathological changes in myocardial infarction are dynamic. The changes start with an inflammatory phase; then, necrotic myocardial fibers are dissolved and absorbed, granulation tissue is gradually formed, and a dense collagen scar is finally formed. Left ventricular remodeling develops after myocardial infarction (MI) and can lead to heart failure. In terminal heart failure, only heart transplantation or implantation of left ventricular assistance devices can be used for efficient treatment. Injection of an injectable hydrogel derived from ventricular extracellular matrix (ECM) in a rat MI model increases the number of endogenous cardiomyocytes in the infarct area and maintains cardiac function without causing arrhythmia [116]. Seif-Naraghi and coworkers developed an injectable hydrogel derived from porcine myocardial extracellular matrix. Two weeks after MI, percutaneous intracardial injection of the myocardial matrix hydrogel was used to treat pigs with MI. Myocardial matrix hydrogel injected after MI can improve heart function, prevent negative LV remodeling, and increase myocardial activity [117] The tissue-level mechanisms of the therapeutic effect of myocardial ECM injection were investigated by using whole transcriptome analysis in a total MI rat model. Principal component analysis of the transcriptome showed that the infarcted myocardium injected with the matrix manifested changes in inflammatory response, decreased myocardial apoptosis, increased new blood vessel formation in the area of infarction, decreased myocardial hypertrophy and fibrosis, changes in the expression of metabolic enzymes, increased expression of cardiac transcription factors, recruitment of progenitor cells, and overall improvement in cardiac function and hemodynamics compared with those in the control group injected with normal saline [118]. These results indicate that dECM hydrogels can promote angiogenesis and maintain cardiac function.

4.2.2. Lung

Increasing incidence of chest tumors, such as lung, breast, and esophageal cancer, enhanced the use of radiotherapy as an important method of treatment of thoracic tumors; therapeutic effect of radiotherapy is positively correlated with radiation dose. However, radiotherapy of thoracic tumors induces radiation lung injury because the surrounding normal lung tissue is susceptible to radiation. Radiation lung injury causes fibrosis in the later stage, cannot be reversed, and leads to severe functional damage to the lung and even death. Epithelial-mesenchymal transition (EMT) plays an important role in radiation-induced pulmonary fibrosis [119]. Therefore, an ECM hydrogel derived from the lung tissue was injected into rat trachea after irradiation to investigate the protective effect on radiation-induced lung injury. The rats were fixed in a supine position on a wooden board to fully expose the chest. The upper boundary of the irradiation field corresponded to the line connecting the midpoints of the two axillas, and the lower boundary of the irradiation field corresponded to the lower edge plane of the lower edge of the xiphoid process; the rest of the body was shielded by a 12 mm lead block. The rats in the IR + NS and IR + ECM groups were irradiated with a 6 MV X-ray linear accelerator at a source-to-surface distance of 100 cm. The dose was 20 Gy, and the dose rate was 3.5 Gy/min. Two treatment groups were injected with 500 μl lung ECM hydrogel or an equivalent amount of normal saline into the trachea half an hour after radiotherapy. Subsequent experiments were performed 4, 8, and 16 weeks after irradiation. The dry/wet weight ratio was used to assess lung congestion and edema. Hematoxylin and eosin staining and Masson trichrome staining were used for histopathological analysis of the lung tissue. Immunohistochemical staining and Western blot analysis were performed to determine the expression of epithelial–mesenchymal transition (EMT)-related proteins in the lung tissues (E-cadherin, α-smooth muscle actin [α-SMA], and vimentin). Additionally, tumor necrosis factor-α (TNF-α), transforming growth factor-β1 (TGF-β1), interleukin-6 (IL-6), hydroxyproline, malondialdehyde (MDA), and superoxide were assayed. The level of superoxide dismutase (SOD) was also evaluated. The results indicated that ECM-derived hydrogels have good cytocompatibility and histocompatibility, and ECM-derived hydrogel treatment has a beneficial effect on histopathological damage and pulmonary edema in the lung. The IR + ECM group had higher E-cadherin expression, and the expression levels of vimentin and α-SMA were lower than those in the IR + NS group; moreover, the dECM hydrogel treatment reduced the hydroxyproline levels. After irradiation, the levels of TNF-α, IL-6, and TGF-β1 were significantly increased. After treatment of irradiated rats with ECM-derived hydrogel, the MDA content was significantly reduced and SOD level was increased. dECM hydrogel treatment reduced radiation-induced lung fibrosis, reduced EMT and radiation-induced lung damage, and improved the survival rate of rats after irradiation [54]. The results indicate that dECM hydrogel as an injectable

biological scaffold has a certain effect on the repair of the damaged tissue.

4.2.3. Brain

ECM hydrogels have been extensively used to repair brain injury and treat stroke. To evaluate the response of the brain tissue to the injection of bladder extracellular matrix hydrogel (UBM), the gel form of UBM was injected into the brain of healthy rats, and the brain tissue response to UBM was examined on days 1, 3, and 21. Application of UBM did not activate microglia, did not increase the number of astrocytes, and did not cause inflammation during neurodegeneration indicating that UBM has no toxic effect on the normal brain. UBM was injected into the ipsilateral hippocampal CA3 area of the rats with brain injury (TBI); the data indicated that the application of UBM reduces the lesion volume and white matter damage, and UBM treatment can lead to a significant recovery of neurological behavior after TBI assessed by vestibular function and an improvement of the motor function. However, UBM treatment did not have a significant effect on cognitive recovery. This study indicated that UBM is biocompatible with the brain tissue and has a certain protective effect in the injured brain [120].

The concentration of UBM determines its penetration in the cavity or tissue in chronic stroke animal models; therefore, UBM concentration influences hydrogel interactions with the host brain [121,122]. Among A concentration of 4 mg/mL achieves a coverage rate of 92% (88–97% range), and a concentration of 8 mg/mL results in a coverage rate of 89%. Too high or too low concentrations are not suitable [121] At a concentration of 8 mg/mL, approximately 60% of infiltrating cells have brain-derived phenotypes, and 30% of the infiltrating cells are peripheral macrophages polarized toward the M2 anti-inflammatory phenotype. Therefore, ECM at a concentration of 8 mg/mL can promote acute endogenous repair responses and can be potentially used to treat stroke [122]. Histologically evaluation of a porcine-derived bladder matrix (UBM)-ECM hydrogel at the concentrations of 0, 3, 4, and 8 mg/mL implanted in a stroke cavity on day 14 after stroke indicated efficient biodegradation of the hydrogel at the concentrations of 3 and 4 mg/mL within 14 days after implantation to promote tissue recovery in the lesion cavity. In contrast, higher concentrations (8 mg/mL) of ECM hydrogel manifested only minor biodegradation and did not lead to tissue recovery. The sensory hydrogel, which is weaker than the brain tissue, provides suitable conditions to promote an endogenous regeneration response, which can restore the tissue in the cavity. This method provides a new means to treat chronic tissue damage caused by stroke and other acute brain injuries in the future [123]. The Thus, injection of dECM hydrogel can promote immune cell infiltration and reduce brain damage.

4.2.4. Spinal cord

After the central nervous system (CNS) is injured, the formation of glial scars inhibits the growth of new axons leading to a lack of regeneration of the central nervous system and poor clinical treatment effects. Extracellular matrix (ECM) was harvested from astrocytes derived from mouse embryonic stem cells (mESC) to prepare a hyaluronic acid (HA) hydrogel that was implanted to treat spinal cord injury in rats. ECM harvested from the protoplasm (gray matter) astrocytes was incorporated into a hydrogel and implanted in rats with spinal cord injury (SCI); this procedure decreased the size of glial scars, increased the penetration of axons into the lesions, and reduced the number of macrophages in the microglia. HA hydrogel supported the transplantation of V2a interneurons and increased the neuronal process area in and around SCI lesions [124]. Injection of a neural dECM hydrogel in rats with spinal cord injury significantly reduced the ratio of M1:M2 macrophages one week later, which was conducive to the regeneration phenotype ($p < 0.05$); the distal tissue interface increased axon extension to acutely regulate the inflammatory environment and support axon growth to promote repair after contusive spinal cord injury [125]. These results indicate that dECM hydrogel can be used as a good biological scaffold and promotes the repair of injured nerve tissue.

4.2.5. Colon

Decellularized porcine small intestinal submucosa ECM hydrogel (ECMH) was delivered locally in a rodent model of ulcerative colitis (UC) to determine whether the biological effects induced by ECM influence a UC rodent model. In this rodent model, ECMH can adhere to the colonic tissue, and ECMH treatment can reduce the clinical symptoms of UC. Animals treated with ECMH have reduced weight loss and reduced hematochezia. Histomorphological analysis indicated that ECMH has a therapeutic effect in this model, and use of ECMH reduced the signs of inflammation and ulceration on days 7 and 14 in the distal and proximal sections of the colon. ECMH treatment can increase the number of E-cadherin positive cells by approximately 50% compared with that in the negative control. ECMH treatment resulted in a decrease in the number of colabeled $CD68^{+}/TNF\alpha^{+}$ cells suggesting that ECMH directly regulates the macrophage response by reducing the number of inflammatory macrophages present in the colon [46]. The results indicate that dECM hydrogel has good biological properties and low immunogenicity, which can provide a basis for subsequent clinical trials.

5. Commercial application of dECM materials

ECM derived products from animal sources have been on the market for more than 20 years and have been used commercially in a variety of applications. ECM materials and scaffolds made from decellularized tissues and organs derived from many animal and human tissues have many clinical applications in wound healing, surgical closure and reinforcement, and tissue reconstruction across large defects. The current clinical products available include: Oasis® (porcine small submucosa, Cook Biotech, Inc., Indiana, USA), GraftJacket® (human dermis, Acelity L.P. Inc., Texas, USA), DermACELL® (human dermis, Novadaq Technologies Inc., Mississauga, Canada), Alloderm® (human dermis, Allergan plc [NYSE: AGN, Dublin, Ireland]), CuffPatch® (Porcine small intestinal submucosa, Arthrotek, Warsaw, Indiana), TissueMend® (Fetal bovine skin, TEI Biosciences, Boston, Massachusetts), Permacol® (Porcine dermis, Tissue Science Laboratories, Covington, Georgia), MatriStem® (Wound Care Matrix, ACell, Inc.), MatriStem® powder (ACell, Inc, Columbia, Maryland), DuoDerm® (ConvaTec, Skillman, New Jersey), NeoForm™ (human dermis, California, USA), Strattice™ (porcine dermis, Allergan plc [NYSE: AGN, Dublin, Ireland]), GraftJacket™ (Human dermi, Wright Medical Technology, Arlington, Tennessee) Restore™ (porcine small intestine [DePuy Orthopedics, Inc., Indiana, USA]), Prima™ Plus (porcine heart valve, Edwards Life Sciences LLC, California,USA), AlloSkin™ AC (human dermis, AlloSource, Centennial, CO, USA), MatriStem® (mucosa of urinary bladder, ACell, Columbia, USA), Biodesign® (small intestine, COOK MEDICAL INC., Bloomington, IN, USA), Lyoplant® (pericardium, Aesculap, Inc., Center Valley, PA, USA) [126–132].

6. Prospects of dECM hydrogels

dECM hydrogels have been widely used as a conventional tissue engineering method; moreover, dECM hydrogels can significantly promote the repair of various damaged tissues and cell culture in vitro. However, the source of tissue dECM, gelation conditions, and various protein concentrations of a hydrogel may influence the structure of dECM hydrogels. For example, restructuring of recently formed sources may be higher than that of the sources formed

some time ago. Viscosity and gel dynamics of a dECM pregel play an important role in its injectability and retention at a specific site to assess successful application in minimally invasive surgery. The therapeutic effects of dECM hydrogels in vivo mainly depend on the biological and mechanical properties of dECM hydrogels. The biological properties of dECM may be determined by the biological materials and animal tissue sources. However, the preparation of dECM hydrogels by adjusting pH, salt or ion concentration, and temperature of the dECM solution can promote gelation only to a certain extent and cannot significantly improve the mechanical properties of dECM hydrogels. Therefore, new functional groups are crosslinked by physical and chemical methods to improve the mechanical properties of dECM hydrogels and promote the repair of the damaged tissues. The application of new crosslinking methods promoted the development of synthetic hydrogels. dECM hydrogel products with better mechanical and biological properties will continue to emerge to provide more options for clinical tissue repair. Future attempts should focus on the use of dECM hydrogels as a drug delivery vehicle to promote in situ repair of the damaged tissues. Complexity of natural ECM indicates that application of one or more biological components is not enough to achieve the characteristics of natural ECM; thus, dECM hydrogels from various tissue sources can be used as biological inks in 3D bioprinting to advance tissue engineering in a new direction.

Availability of data and material

Not applicable.

Funding sources

This work was supported by the Project of Innovation and Entrepreneurship training Program for College students of Hunan Province, in 2018 (No. 20180138) and Project of College Students' Research Learning and Innovative Experimental, University of South China, in 2019 (No. 20192908).

Author contributions

Wenhui Zhang, Aoling Du and Shenghua Chen wrote the manuscript. Shun Liu and Mingyue Lv designed the figures and tables. All authors read and approved the manuscript.

Declaration of competing interest

The authors declare that they have no competing interests.

Acknowledgments

Not applicable.

References

[1] Ullah I, Busch JF, Rabien A, Ergün B, Stamm C, Knosalla C, et al. Adult tissue extracellular matrix determines tissue specification of human iPSC-derived embryonic stage mesodermal precursor cells. Adv Sci 2020;7:1901198.
[2] Pattar SS, Fatehi Hassanabad A, Fedak PWM. Acellular extracellular matrix bioscaffolds for cardiac repair and regeneration. Front Cell Dev Biol 2019;7:63.
[3] Starzl TE, Marchioro TL, Vonkaulla KN, Hermann G, Brittain RS, Waddell WR. Homotransplantation of the liver in humans. Surg Gynecol Obstet 1963;117:659–76.
[4] Ochando J, Fayad ZA, Madsen JC, Netea MG, Mulder WJM. Trained immunity in organ transplantation. Am J Transplant 2020;20:10–8.
[5] Li M, Zhang C, Mao Y, Zhong Y, Zhao J. A cell-engineered small intestinal submucosa-based bone Mimetic construct for bone regeneration. Tissue Eng A 2018;24:1099–111.
[6] Kim H, Bae C, Kook YM, Koh WG, Lee K, Park MH. Mesenchymal stem cell 3D encapsulation technologies for biomimetic microenvironment in tissue regeneration. Stem Cell Res Ther 2019;10:51.
[7] Badylak SF, Gilbert TW. Immune response to biologic scaffold materials. Semin Immunol 2008;20:109–16.
[8] Gilbert TW, Sellaro TL, Badylak SF. Decellularization of tissues and organs. Biomaterials 2006;27:3675–83.
[9] Kim BS, Kim H, Gao G, Jang J, Cho DW. Decellularized extracellular matrix: a step towards the next generation source for bioink manufacturing. Biofabrication 2017;9:034104.
[10] Crapo PM, Gilbert TW, Badylak SF. An overview of tissue and whole organ decellularization processes. Biomaterials 2011;32:3233–43.
[11] Khan AA, Vishwakarma SK, Bardia A, Venkateshwarulu J. Repopulation of decellularized whole organ scaffold using stem cells: an emerging technology for the development of neo-organ. J Artif Organs 2014;17:291–300.
[12] Spang MT, Christman KL. Extracellular matrix hydrogel therapies: in vivo applications and development. Acta Biomater 2018;68:1–14.
[13] Roorda WE, Boddé HE, De Boer AG, Bouwstra JA, Junginer HE. Synthetic hydrogels as drug delivery systems. Pharm Weekbl Sci 1986;8:165–89.
[14] Kabirian F, Mozafari M. Decellularized ECM-derived bioinks: prospects for the future. Methods 2020;171:108–18.
[15] Wichterle O, Lím D. Hydrophilic gels for biological use. Nature 1960;185:117–8.
[16] Glowacki J, Mizuno S. Collagen scaffolds for tissue engineering. Biopolymers 2008;89:338–44.
[17] Sakai S, Hirose K, Taguchi K, Ogushi Y, Kawakami K. An injectable, in situ enzymatically gellable, gelatin derivative for drug delivery and tissue engineering. Biomaterials 2009;30:3371–7.
[18] Baier Leach J, Bivens KA, Patrick Jr CW, Schmidt CE. Photocrosslinked hyaluronic acid hydrogels: natural, biodegradable tissue engineering scaffolds. Biotechnol Bioeng 2003;82:578–89.
[19] Ramamurthi A, Vesely I. Ultraviolet light-induced modification of crosslinked hyaluronan gels. J Biomed Mater Res A 2003;66:317–29.
[20] Mol A, van Lieshout MI, Dam-de Veen CG, Neuenschwander S, Hoerstrup SP, Baaijens FP, et al. Fibrin as a cell carrier in cardiovascular tissue engineering applications. Biomaterials 2005;26:3113–21.
[21] Kuo CK, Ma PX. Ionically crosslinked alginate hydrogels as scaffolds for tissue engineering: part 1. Structure, gelation rate and mechanical properties. Biomaterials 2001;22:511–21.
[22] Kim IY, Seo SJ, Moon HS, Yoo MK, Park IY, Kim BC, et al. Chitosan and its derivatives for tissue engineering applications. Biotechnol Adv 2008;26:1–21.
[23] Lee J, Cuddihy MJ, Kotov NA. Three-dimensional cell culture matrices: state of the art. Tissue Eng B Rev 2008;14:61–86.
[24] Zhu J. Bioactive modification of poly(ethylene glycol) hydrogels for tissue engineering. Biomaterials 2010;31:4639–56.
[25] Nuttelman CR, Rice MA, Rydholm AE, Salinas CN, Shah DN, Anseth KS. Macromolecular monomers for the synthesis of hydrogel niches and their application in cell encapsulation and tissue engineering. Prog Polym Sci 2008;33:167–79.
[26] Brandl F, Sommer F, Goepferich A. Rational design of hydrogels for tissue engineering: impact of physical factors on cell behavior. Biomaterials 2007;28:134–46.
[27] Buxton AN, Zhu J, Marchant R, West JL, Yoo JU, Johnstone B. Design and characterization of poly(ethylene glycol) photopolymerizable semi-interpenetrating networks for chondrogenesis of human mesenchymal stem cells. Tissue Eng 2007;13:2549–60.
[28] Beamish JA, Zhu J, Kottke-Marchant K, Marchant RE. The effects of monoacrylated poly(ethylene glycol) on the properties of poly(ethylene glycol) diacrylate hydrogels used for tissue engineering. J Biomed Mater Res A 2010;92:441–50.
[29] Yang F, Williams CG, Wang DA, Lee H, Manson PN, Elisseeff J. The effect of incorporating RGD adhesive peptide in polyethylene glycol diacrylate hydrogel on osteogenesis of bone marrow stromal cells. Biomaterials 2005;26:5991–8.
[30] Schmedlen RH, Masters KS, West JL. Photocrosslinkable polyvinyl alcohol hydrogels that can be modified with cell adhesion peptides for use in tissue engineering. Biomaterials 2002;23:4325–32.
[31] Woerly S, Pinet E, de Robertis L, Van Diep D, Bousmina M. Spinal cord repair with PHPMA hydrogel containing RGD peptides (NeuroGel). Biomaterials 2001;22:1095–111.
[32] Vihola H, Laukkanen A, Valtola L, Tenhu H, Hirvonen J. Cytotoxicity of thermosensitive polymers poly(N-isopropylacrylamide), poly(N-vinylcaprolactam) and amphiphilically modified poly(N-vinylcaprolactam). Biomaterials 2005;26:3055–64.
[33] Hunt NC, Grover LM. Cell encapsulation using biopolymer gels for regenerative medicine. Biotechnol Lett 2010;32:733–42.
[34] Higuchi A, Aoki N, Yamamoto T, Miyazaki T, Fukushima H, Tak TM, et al. Temperature-induced cell detachment on immobilized pluronic surface. J Biomed Mater Res A 2006;79:380–92.
[35] Freytes DO, Martin J, Velankar SS, Lee AS, Badylak SF. Preparation and rheological characterization of a gel form of the porcine urinary bladder matrix. Biomaterials 2008;29:1630–7.
[36] Saldin LT, Cramer MC, Velankar SS, White LJ, Badylak SF. Extracellular matrix hydrogels from decellularized tissues: structure and function. Acta Biomater 2017;49:1–15.

[37] Seo Y, Jung Y, Kim SH. Decellularized heart ECM hydrogel using supercritical carbon dioxide for improved angiogenesis. Acta Biomater 2018;67:270–81.
[38] Jang J, Park HJ, Kim SW, Kim H, Park JY, Na SJ, et al. 3D printed complex tissue construct using stem cell-laden decellularized extracellular matrix bioinks for cardiac repair. Biomaterials 2017;112:264–74.
[39] Baghalishahi M, Efthekhar-Vaghefi SH, Piryaei A, Nematolahi-Mahani SN, Mollaei HR, Sadeghi Y. Cardiac extracellular matrix hydrogel together with or without inducer cocktail improves human adipose tissue-derived stem cells differentiation into cardiomyocyte-like cells. Biochem Biophys Res Commun 2018;502:215–25.
[40] Hiraki HL, Nagao RJ, Himmelfarb J, Zheng Y. Fabricating a kidney cortex extracellular matrix-derived hydrogel. J Vis Exp 2018;140:58314.
[41] Su J, Satchell SC, Shah RN, Wertheim JA. Kidney decellularized extracellular matrix hydrogels: rheological characterization and human glomerular endothelial cell response to encapsulation. J Biomed Mater Res A 2018;106:2448–62.
[42] Saheli M, Sepantafar M, Pournasr B, Farzaneh Z, Vosough M, Piryaei A, et al. Three-dimensional liver-derived extracellular matrix hydrogel promotes liver organoids function. J Cell Biochem 2018;119:4320–33.
[43] Gaetani R, Aude S, DeMaddalena LL, Strassle H, Dzieciatkowska M, Wortham M, et al. Evaluation of different decellularization protocols on the generation of pancreas-derived hydrogels. Tissue Eng C Methods 2018;24:697–708.
[44] Naranjo JD, Saldin LT, Sobieski E, Quijano LM, Hill RC, Chan PG, et al. Esophageal extracellular matrix hydrogel mitigates metaplastic change in a dog model of Barrett's esophagus. Sci Adv 2020;6:eaba4526.
[45] Giobbe GG, Crowley C, Luni C, Campinoti S, Khedr M, Kretzschmar K, et al. Extracellular matrix hydrogel derived from decellularized tissues enables endodermal organoid culture. Nat Commun 2019;10:5658.
[46] Keane TJ, Dziki J, Sobieski E, Smoulder A, Castleton A, Turner N, et al. Restoring mucosal Barrier function and Modifying macrophage phenotype with an extracellular matrix hydrogel: potential Therapy for ulcerative colitis. J Crohns Colitis 2017;11:360–8.
[47] Zhong G, Yao J, Huang X, Luo Y, Wang M, Han J, et al. Injectable ECM hydrogel for delivery of BMSCs enabled full-thickness meniscus repair in an orthotopic rat model. Bioact Mater 2020;5:871–9.
[48] Wu J, Ding Q, Dutta A, Wang Y, Huang YH, Weng H, et al. An injectable extracellular matrix derived hydrogel for meniscus repair and regeneration. Acta Biomater 2015;16:49–59.
[49] Lin T, Liu S, Chen S, Qiu S, Rao Z, Liu J, et al. Hydrogel derived from porcine decellularized nerve tissue as a promising biomaterial for repairing peripheral nerve defects. Acta Biomater 2018;73:326–38.
[50] Prest TA, Yeager E, LoPresti ST, Zygelyte E, Martin MJ, Dong L, et al. Nerve-specific, xenogeneic extracellular matrix hydrogel promotes recovery following peripheral nerve injury. J Biomed Mater Res A 2018;106:450–9.
[51] Medberry CJ, Crapo PM, Siu BF, Carruthers CA, Wolf MT, Nagarkar SP, et al. Hydrogels derived from central nervous system extracellular matrix. Biomaterials 2013;34:1033–40.
[52] Tan QW, Zhang Y, Luo JC, Zhang D, Xiong BJ, Yang JQ, et al. Hydrogel derived from decellularized porcine adipose tissue as a promising biomaterial for soft tissue augmentation. J Biomed Mater Res A 2017;105:1756–64.
[53] Mahoney CM, Kelmindi-Doko A, Snowden MJ, Peter Rubin J, Marra KG. Adipose derived delivery vehicle for encapsulated adipogenic factors. Acta Biomater 2017;58:26–33.
[54] Zhou J, Wu P, Sun H, Zhou H, Zhang Y, Xiao Z. Lung tissue extracellular matrix-derived hydrogels protect against radiation-induced lung injury by suppressing epithelial-mesenchymal transition. J Cell Physiol 2020;235:2377–88.
[55] Hussey GS, Nascari DG, Saldin LT, Kolich B, Lee YC, Crum RJ, et al. Ultrasonic cavitation to prepare ECM hydrogels. Acta Biomater 2020;108:77–86.
[56] Zhu W, Cao L, Song C, Pang Z, Jiang H, Guo C. Cell-derived decellularized extracellular matrix scaffolds for articular cartilage repair. Int J Artif Organs 2021;44(4):269–81.
[57] Fitzpatrick LE, McDevitt TC. Cell-derived matrices for tissue engineering and regenerative medicine applications. Biomater Sci 2015;3(1):12–24.
[58] Lin H, Yang G, Tan J, Tuan RS. Influence of decellularized matrix derived from human mesenchymal stem cells on their proliferation, migration and multi-lineage differentiation potential. Biomaterials 2012;33:4480–9.
[59] Hoshiba T, Tanaka M. Decellularized matrices as in vitro models of extracellular matrix in tumor tissues at different malignant levels: mechanism of 5-fluorouracil resistance in colorectal tumor cells. Biochim Biophys Acta 2016;1863:2749–57.
[60] Denner J, Tönjes RR. Infection barriers to successful xenotransplantation focusing on porcine endogenous retroviruses. Clin Microbiol Rev 2012;25:318–43.
[61] Shin YJ, Shafranek RT, Tsui JH, Walcott J, Nelson A, Kim DH. 3D bioprinting of mechanically tuned bioinks derived from cardiac decellularized extracellular matrix. Acta Biomater 2021;119:75–88.
[62] Pokrywczynska M, Gubanska I, Drewa G, Drewa T. Application of bladder acellular matrix in urinary bladder regeneration: the state of the art and future directions. BioMed Res Int 2015;2015:613439.
[63] Toprakhisar B, Nadernezhad A, Bakirci E, Khani N, Skvortsov GA, Koc B. Development of bioink from decellularized tendon extracellular matrix for 3D bioprinting. Macromol Biosci 2018;18:e1800024.
[64] Vishwakarma SK, Bhavani PG, Bardia A, Abkari A, Murthy GS, Venkateshwarulu J, et al. Preparation of natural three-dimensional goat kidney scaffold for the development of bioartificial organ. Indian J Nephrol 2014;24:372–5.
[65] Gupta SK, Dinda AK, Potdar PD, Mishra NC. Fabrication and characterization of scaffold from cadaver goat-lung tissue for skin tissue engineering applications. Mater Sci Eng C Mater Biol Appl 2013;33:4032–8.
[66] Geerts S, Ozer S, Jaramillo M, Yarmush ML, Uygun BE. Nondestructive methods for monitoring cell removal during rat liver decellularization. Tissue Eng C Methods 2016;22:671–8.
[67] Ren X, Moser PT, Gilpin SE, Okamoto T, Wu T, Tapias LF, et al. Engineering pulmonary vasculature in decellularized rat and human lungs. Nat Biotechnol 2015;33:1097–102.
[68] Skardal A, Devarasetty M, Kang HW, Mead I, Bishop C, Shupe T, et al. A hydrogel bioink toolkit for mimicking native tissue biochemical and mechanical properties in bioprinted tissue constructs. Acta Biomater 2015;25:24–34.
[69] Jang J, Kim TG, Kim BS, Kim SW, Kwon SM, Cho DW. Tailoring mechanical properties of decellularized extracellular matrix bioink by vitamin B2-induced photo-crosslinking. Acta Biomater 2016;33:88–95.
[70] Pati F, Ha DH, Jang J, Han HH, Rhie JW, Cho DW. Biomimetic 3D tissue printing for soft tissue regeneration. Biomaterials 2015;62:164–75.
[71] Nirea KG, Meuwissen TH. Improving production efficiency in the presence of genotype by environment interactions in pig genomic selection breeding programmes. J Anim Breed Genet 2017;134:119–28.
[72] Kimsa MC, Strzalka-Mrozik B, Kimsa MW, Gola J, Nicholson P, Lopata K, et al. Porcine endogenous retroviruses in xenotransplantation – molecular aspects. Viruses 2014;6:2062–83.
[73] Tottey S, Johnson SA, Crapo PM, Reing JE, Zhang L, Jiang H, et al. The effect of source animal age upon extracellular matrix scaffold properties. Biomaterials 2011;32:128–36.
[74] Duisit J, Amiel H, Wüthrich T, Taddeo A, Dedriche A, Destoop V, et al. Perfusion-decellularization of human ear grafts enables ECM-based scaffolds for auricular vascularized composite tissue engineering. Acta Biomater 2018;73:339–54.
[75] Porzionato A, Stocco E, Barbon S, Grandi F, Macchi V, De Caro R. Tissue-engineered grafts from human decellularized extracellular matrices: a systematic review and future perspectives. Int J Mol Sci 2018;19.
[76] Meran L, Massie I, Campinoti S, Weston AE, Gaifulina R, Tullie L, et al. Engineering transplantable jejunal mucosal grafts using patient-derived organoids from children with intestinal failure. Nat Med 2020;26:1593–601.
[77] Garreta E, de Oñate L, Fernández-Santos ME, Oria R, Tarantino C, Climent AM, et al. Myocardial commitment from human pluripotent stem cells: rapid production of human heart grafts. Biomaterials 2016;98:64–78.
[78] Guyette JP, Charest JM, Mills RW, Jank BJ, Moser PT, Gilpin SE, et al. Bioengineering human myocardium on native extracellular matrix. Circ Res 2016;118:56–72.
[79] Chen Y, Chen J, Zhang Z, Lou K, Zhang Q, Wang S, et al. Current advances in the development of natural meniscus scaffolds: innovative approaches to decellularization and recellularization. Cell Tissue Res 2017;370:41–52.
[80] Schneider C, Lehmann J, van Osch GJ, Hildner F, Teuschl A, Monforte X, et al. Systematic comparison of protocols for the preparation of human articular cartilage for use as scaffold material in cartilage tissue engineering. Tissue Eng C Methods 2016;22:1095–107.
[81] Sandmann GH, Eichhorn S, Vogt S, Adamczyk C, Aryee S, Hoberg M, et al. Generation and characterization of a human acellular meniscus scaffold for tissue engineering. J Biomed Mater Res A 2009;91:567–74.
[82] Hassanpour A, Talaei-Khozani T, Kargar-Abarghouei E, Razban V, Vojdani Z. Decellularized human ovarian scaffold based on a sodium lauryl ester sulfate (SLES)-treated protocol, as a natural three-dimensional scaffold for construction of bioengineered ovaries. Stem Cell Res Ther 2018;9:252.
[83] Han TT, Toutounji S, Amsden BG, Flynn LE. Adipose-derived stromal cells mediate in vivo adipogenesis, angiogenesis and inflammation in decellularized adipose tissue bioscaffolds. Biomaterials 2015;72:125–37.
[84] Brown CF, Yan J, Han TT, Marecak DM, Amsden BG, Flynn LE. Effect of decellularized adipose tissue particle size and cell density on adipose-derived stem cell proliferation and adipogenic differentiation in composite methacrylated chondroitin sulphate hydrogels. Biomed Mater 2015;10:045010.
[85] Peloso A, Urbani L, Cravedi P, Katari R, Maghsoudlou P, Fallas ME, et al. The human pancreas as a source of Protolerogenic extracellular matrix scaffold for a new-generation bioartificial Endocrine pancreas. Ann Surg 2016;264:169–79.
[86] Peloso A, Petrosyan A, Da Sacco S, Booth C, Zambon JP, O'Brien T, et al. Renal extracellular matrix scaffolds from discarded kidneys maintain glomerular morphometry and vascular resilience and retains critical growth factors. Transplantation 2015;99:1807–16.
[87] Mattei G, Magliaro C, Pirone A, Ahluwalia A. Decellularized human liver is too heterogeneous for designing a generic extracellular matrix mimic hepatic scaffold. Artif Organs 2017;41:e347–55.
[88] Milan PB, Lotfibakhshaiesh N, Joghataie MT, Ai J, Pazouki A, Kaplan DL, et al. Accelerated wound healing in a diabetic rat model using decellularized dermal matrix and human umbilical cord perivascular cells. Acta Biomater 2016;45:234–46.

[89] Matoug-Elwerfelli M, Duggal MS, Nazzal H, Esteves F, Raïf E. A biocompatible decellularized pulp scaffold for regenerative endodontics. Int Endod J 2018;51:663–73.
[90] Nichols JE, La Francesca S, Vega SP, Niles JA, Argueta LB, Riddle M, et al. Giving new life to old lungs: methods to produce and assess whole human paediatric bioengineered lungs. J Tissue Eng Regen Med 2017;11:2136–52.
[91] Wolf MT, Daly KA, Brennan-Pierce EP, Johnson SA, Carruthers CA, D'Amore A, et al. A hydrogel derived from decellularized dermal extracellular matrix. Biomaterials 2012;33:7028–38.
[92] Ungerleider JL, Johnson TD, Rao N, Christman KL. Fabrication and characterization of injectable hydrogels derived from decellularized skeletal and cardiac muscle. Methods 2015;84:53–9.
[93] Lewis PL, Su J, Yan M, Meng F, Glaser SS, Alpini GD, et al. Complex bile duct network formation within liver decellularized extracellular matrix hydrogels. Sci Rep 2018;8:12220.
[94] Dzobo K, Motaung K, Adesida A. Recent trends in decellularized extracellular matrix bioinks for 3D printing: an updated review. Int J Mol Sci 2019;20.
[95] Zhang Y, He Y, Bharadwaj S, Hammam N, Carnagey K, Myers R, et al. Tissue-specific extracellular matrix coatings for the promotion of cell proliferation and maintenance of cell phenotype. Biomaterials 2009;30:4021–8.
[96] Allen RA, Seltz LM, Jiang H, Kasick RT, Sellaro TL, Badylak SF, et al. Adrenal extracellular matrix scaffolds support adrenocortical cell proliferation and function in vitro. Tissue Eng A 2010;16:3363–74.
[97] Brennan EP, Tang X-H, Stewart-Akers AM, Gudas LJ, Badylak SF. Chemoattractant activity of degradation products of fetal and adult skin extracellular matrix for keratinocyte progenitor cells. J Tissue Eng Regen Med 2008;2:491–8.
[98] Sellaro TL, Ranade A, Faulk DM, McCabe GP, Dorko K, Badylak SF, et al. Maintenance of human hepatocyte function in vitro by liver-derived extracellular matrix gels. Tissue Eng A 2010;16:1075–82.
[99] Lewis PL, Yan M, Su J, Shah RN. Directing the growth and alignment of biliary epithelium within extracellular matrix hydrogels. Acta Biomater 2019;85:84–93.
[100] Kang HW, Lee SJ, Ko IK, Kengla C, Yoo JJ, Atala A. A 3D bioprinting system to produce human-scale tissue constructs with structural integrity. Nat Biotechnol 2016;34:312–9.
[101] Derby B. Printing and prototyping of tissues and scaffolds. Science 2012;338:921–6.
[102] Murphy SV, Atala A. 3D bioprinting of tissues and organs. Nat Biotechnol 2014;32:773–85.
[103] Highley CB, Song KH, Daly AC, Burdick JA. Jammed microgel inks for 3D printing applications. Adv Sci 2019;6:1801076.
[104] Kolesky DB, Homan KA, Skylar-Scott MA, Lewis JA. Three-dimensional bioprinting of thick vascularized tissues. Proc Natl Acad Sci U S A 2016;113:3179–84.
[105] Trachsel L, Johnbosco C, Lang T, Benetti EM, Zenobi-Wong M. Double-network hydrogels including enzymatically crosslinked poly-(2-alkyl-2-oxazoline)s for 3D bioprinting of cartilage-engineering constructs. Biomacromolecules 2019;20:4502–11.
[106] Motealleh A, Çelebi-Saltik B, Ermis N, Nowak S, Khademhosseini A, Kehr NS. 3D printing of step-gradient nanocomposite hydrogels for controlled cell migration. Biofabrication 2019;11:045015.
[107] Gao T, Gillispie GJ, Copus JS, Pr AK, Seol YJ, Atala A, et al. Optimization of gelatin-alginate composite bioink printability using rheological parameters: a systematic approach. Biofabrication 2018;10:034106.
[108] Kiyotake EA, Douglas AW, Thomas EE, Nimmo SL, Detamore MS. Development and quantitative characterization of the precursor rheology of hyaluronic acid hydrogels for bioprinting. Acta Biomater 2019;95:176–87.
[109] Lee A, Hudson AR, Shiwarski DJ, Tashman JW, Hinton TJ, Yerneni S, et al. 3D bioprinting of collagen to rebuild components of the human heart. Science 2019;365:482–7.
[110] Pati F, Jang J, Ha DH, Won Kim S, Rhie JW, Shim JH, et al. Printing three-dimensional tissue analogues with decellularized extracellular matrix bioink. Nat Commun 2014;5:3935.
[111] Choudhury D, Tun HW, Wang T, Naing MW. Organ-derived decellularized extracellular matrix: a game changer for bioink manufacturing? Trends Biotechnol 2018;36:787–805.
[112] Abaci A, Guvendiren M. Designing decellularized extracellular matrix-based bioinks for 3D bioprinting. Adv Healthc Mater 2020;9:e2000734.
[113] Ali M, Pr AK, Yoo JJ, Zahran F, Atala A, Lee SJ. A photo-crosslinkable kidney ECM-derived bioink Accelerates renal tissue formation. Adv Healthc Mater 2019;8:e1800992.
[114] Mollica PA, Booth-Creech EN, Reid JA, Zamponi M, Sullivan SM, Palmer XL, et al. 3D bioprinted mammary organoids and tumoroids in human mammary derived ECM hydrogels. Acta Biomater 2019;95:201–13.
[115] Ferreira LP, Gaspar VM, Mano JF. Decellularized extracellular matrix for bioengineering Physiomimetic 3D in vitro tumor models. Trends Biotechnol 2020;38:1397–414.
[116] Singelyn JM, Sundaramurthy P, Johnson TD, Schup-Magoffin PJ, Hu DP, Faulk DM, et al. Catheter-deliverable hydrogel derived from decellularized ventricular extracellular matrix increases endogenous cardiomyocytes and preserves cardiac function post-myocardial infarction. J Am Coll Cardiol 2012;59:751–63.
[117] Seif-Naraghi SB, Singelyn JM, Salvatore MA, Osborn KG, Wang JJ, Sampat U, et al. Safety and efficacy of an injectable extracellular matrix hydrogel for treating myocardial infarction. Sci Transl Med 2013;5:173–82.
[118] Wassenaar JW, Gaetani R, Garcia JJ, Braden RL, Luo CG, Huang D, et al. Evidence for mechanisms underlying the functional benefits of a myocardial matrix hydrogel for post-MI treatment. J Am Coll Cardiol 2016;67:1074–86.
[119] Bartis D, Mise N, Mahida RY, Eickelberg O, Thickett DR. Epithelial-mesenchymal transition in lung development and disease: does it exist and is it important? Thorax 2014;69:760–5.
[120] Zhang L, Zhang F, Weng Z, Brown BN, Yan H, Ma XM, et al. Effect of an inductive hydrogel composed of urinary bladder matrix upon functional recovery following traumatic brain injury. Tissue Eng A 2013;19:1909–18.
[121] Massensini AR, Ghuman H, Saldin LT, Medberry CJ, Keane TJ, Nicholls FJ, et al. Concentration-dependent rheological properties of ECM hydrogel for intracerebral delivery to a stroke cavity. Acta Biomater 2015;27:116–30.
[122] Ghuman H, Massensini AR, Donnelly J, Kim SM, Medberry CJ, Badylak SF, et al. ECM hydrogel for the treatment of stroke: characterization of the host cell infiltrate. Biomaterials 2016;91:166–81.
[123] Ghuman H, Mauney C, Donnelly J, Massensini AR, Badylak SF, Modo M. Biodegradation of ECM hydrogel promotes endogenous brain tissue restoration in a rat model of stroke. Acta Biomater 2018;80:66–84.
[124] Thompson RE, Pardieck J, Smith L, Kenny P, Crawford L, Shoichet M, et al. Effect of hyaluronic acid hydrogels containing astrocyte-derived extracellular matrix and/or V2a interneurons on histologic outcomes following spinal cord injury. Biomaterials 2018;162:208–23.
[125] Cornelison RC, Gonzalez-Rothi EJ, Porvasnik SL, Wellman SM, Park JH, Fuller DD, et al. Injectable hydrogels of optimized acellular nerve for injection in the injured spinal cord. Biomed Mater 2018;13:034110.
[126] Liu YC, Chhabra N, Houser SM. Novel treatment of a septal ulceration using an extracellular matrix scaffold (septal ulceration treatment using ECM). Am J Otolaryngol 2016;37:195–8.
[127] Riganti JM, Ciotola F, Amenabar A, Craiem D, Graf S, Badaloni A, et al. Urinary bladder matrix scaffolds strengthen esophageal hiatus repair. J Surg Res 2016;204:344–50.
[128] Abu Saleh WK, Al Jabbari O, Ramlawi B, Bruckner BA, Loebe M, Reardon MJ. Case report: cardiac tumor Resection and repair with porcine xenograft. Methodist Debakey Cardiovasc J 2016;12:116–8.
[129] Abu Saleh WK, Al Jabbari O, Ramlawi B, Bruckner BA, Loebe M, Reardon MJ. Right atrial tumor resection and reconstruction with use of an acellular porcine bladder membrane. Tex Heart Inst J 2016;43:175–7.
[130] Rommer EA, Peric M, Wong A. Urinary bladder matrix for the treatment of recalcitrant nonhealing radiation wounds. Adv Skin Wound Care 2013;26:450–5.
[131] Lecheminant J, Field C. Porcine urinary bladder matrix: a retrospective study and establishment of protocol. J Wound Care 2012;21(476):478–80. 482.
[132] Guruswamy Damodaran R, Vermette P. Tissue and organ decellularization in regenerative medicine. Biotechnol Prog 2018;34:1494–505.